1,176,339

PATENT SPECIFICATION

NO DRAWINGS

1,176,339

Date of Application and filing Complete Specification: 23 Dec., 1966.

No. 57677/66.

Application made in United States of America (No. 516708) on 27 Dec., 1965.

Complete Specification Published: 1 Jan., 1970.

Index at acceptance: —**C2** C(1E7B2, 1E7C2, 1E7E1, 1E7H2, 1E7N3, 1E7P3, 1K2A2, 1K2B, 1K2C2, 3A7V1A2, 3A7V1E1, 3A7V1E2, 3A7V1J1, 3A7V1K1, 3A7V1L, 3A7V3A2, 3A7V3E1, 3A7V3E2, 3A7V3G1, 3A7V3J3, 3C5A2, 3C5C3, 3C5E2, 22Y, 220, 226, 227, 29Y, 29X, 31Y, 313, 32Y, 323, 338, 36Y, 364, 366, 368, 491, 620, 624, 628, 65X, 650, 658, 662, 79Y, 790, LQ)

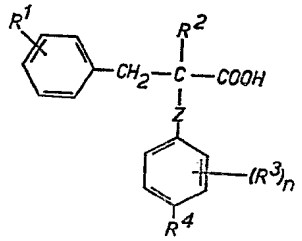
International Classification: —**C 07 c 63/52, 69/76**

COMPLETE SPECIFICATION

Hydrocinnamic Acid Compounds and Processes for making them

We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention concerns novel α-substituted hydrocinnamic acids and processes for making said compounds. The new compounds provided by this invention are of the formula:



(I)

wherein

R^1 is hydrogen, a halogen atom or a C_1—C_4 alkyl or C_1—C_4 alkoxy group;

R^2 is hydrogen or a methyl group;

R^3 is a halogen atom;

n is 0 or 1;

R^4 is hydrogen, a halogen atom, or a C_1—C_4 alkyl, C_1—C_4 alkoxy, phenyl or phenoxy group; and

Z is oxygen or sulfur;

the salts thereof with alkali metals or alkaline earth metals, or ammonium salts thereof; and

the C_1—C_4 alkyl or di(C_1—C_4 alkyl) amino-C_1—C_4 alkyl esters thereof, excluding the 2-dimethylaminoethyl ester of α-phenoxyhydrocinnamic acid and excluding the free-acid compound when n is 1 and R^2 and R^4 are hydrogen and the free-acid compound when n is 0, R^2 is hydrogen and R^4 is halogen.

C_1—C_4 alkyl can be illustratively methyl, ethyl, *n*-propyl, isopropyl, n-butyl, *sec.*-butyl, or *t*-butyl.

Di (C_1—C_4 alkyl)amino-C_1—C_4 alkyl can be illustratively dimethylaminoethyl, diethylaminoethyl, dimethylaminopropyl or di-*n*-propylaminoethyl.

The halogen can be illustratively chlorine, bromine, iodine or fluorine.

C_1—C_4 alkoxy can be illustratively methoxy, ethoxy, *n*-propoxy, *n*-butoxy, isopropoxy, isobutoxy, *sec.*-butoxy, and *t*-butoxy.

Among the compounds of the invention are the following:

α - Methyl - α - (*m* - tolyloxy) - 3 - chlorohydrocinnamic acid

α - Methyl - α - (*m* - anisyloxy) - 2 - bromohydrocinnamic acid

α - Methyl - α (*m* - chlorophenylmercapto) - 3 - methylhydrocinnamic acid.

α - Methyl - α - (2,4 - dibromophenylmercapto) - 2 - bromohydrocinnamic acid

α - Methyl - α - (4 - bromophenoxy) - 2 - methylhydrocinnamic acid.

α - Methyl - α - (4 - phenoxyphenoxy) - 3 - bromohydrocinnamic acid

α - (4 - Phenylphenylmercapto) - 2 - chlorohydrocinnamic acid

α - Methyl - 2 - (chlorophenylmercapto) - 2 - bromohydrocinnamic acid

α - Methyl - α - (4 - methoxyphenoxy) - 2 - chlorohydrocinnamic acid, sodium salt

α - (4 - Chlorophenylmercapto) - 3 - chlorohydrocinnamic acid, potassium salt

α - Methyl - α - (4 - chlorophenylmercapto) - 3 - methoxyhydrocinnamic acid, ammonium salt

α - Methyl - α - (2,4 - dichlorophenoxy) hydrocinnamic acid, calcium salt

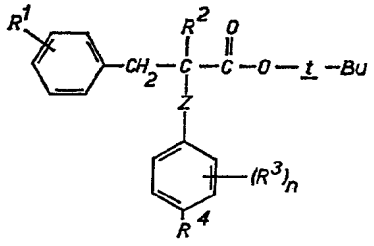
Ethyl α - methyl - α - (4 - chlorophenoxy)hydrocinnamate

The novel compounds of this invention have useful pharmacological properties. When administered orally to rats, they demonstrate the significant and highly desirable property of reducing the serum cholesterol and triglyceride levels. Some of the subject compounds also manifest interesting activity as blood sugar-lowering agents when administered orally to rats by the method of Root et al., *Diabetes 8*, 7 (1959).

The active compounds of this invention are readily formulated for oral administration by admixture with suitable excipients and manufactured by known means into tablets, capsules, suspensions, emulsions, dispersible powders, syrups or elixirs.

Accordingly, a further provision of the invention is pharmaceutical compositions which comprise the new compounds as defined above in admixture with a pharmaceutically acceptable carrier.

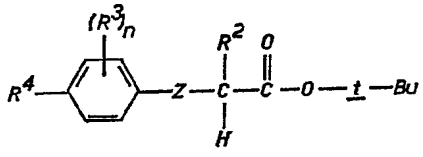
A still further provision of the invention are the novel esters of the formula:



(II)

wherein R^1, R^2, R^3, R^4, n and Z have the same meaning as above and *t*-Bu represents a tertiary-butyl radical.

The above esters of formula (II) can be formed as described below by using intermediate *t*-butyl esters of the formula:



(III)

wherein R^2, R^3, R^4, n Z and *t*-Bu have the same meanings as above.

It is also within the purview of the invention to provide a process for preparing the new compounds of formula (I) and the above defined salts and esters thereof, which comprises hydrolyzing an ester of formula (II), and, if desired, converting the resulting acid into a salt or ester thereof of the class defined above.

A still further provision of the invention is a process for preparing the novel esters of formula (II) which comprises mixing an alkali metal amide and a benzyl halide in an inert organic solvent with a *t*-butyl α-(aryloxy)propionate, *t*-butyl α-(arylmercapto)propionate, *t*-butyl aryloxyacetate, or *t*-butyl arylmercaptoacetate, and exposing the resulting mixture to about ambient room temperature for a time sufficient to complete the reaction thereof.

Still another provision of the invention is a process for preparing the novel esters of formula (II) as described above wherein the propionate or acetate is formed by reacting an appropriate phenol or thiophenol in the presence of a base and an inert solvent with an appropriate C_1—C_4 alkyl α-halopropionate, α-halopropionic acid or *t*-butyl chloroacetate.

The novel hydrocinnamic acids of this invention are prepared by a synthesis which makes them available in good yields. The synthesis utilizes as the key intermediate a *t*-butyl ester of the formula III, *supra*, which can be obtained by one of the following procedures:

When R^2 represents methyl in the generic formula (III), supra, a lower-alkyl α-halopropionate, for example, ethyl α-bromopropionate or *t*-butyl α-bromopropionate, is mixed with an appropriate phenol or thiophenol in the presence of a base in a suitable solvent to yield a lower-alkyl α-(aryloxy or arylmercapto)propionate. Suitable bases include potassium carbonate, sodium carbonate, sodium hydroxide and potassium hydroxide, while suitable solvents include acetone, ethanol and benzene. In the case where the ester obtained is an ethyl α-(aryloxy or arylmercapto)propionate, it can be suitably purified by distillation at reduced pressure, or, omitting the distillation, can be conveniently hydrolyzed under basic conditions to yield an α-(aryloxy or arylmercapto) propionic acid. This acid is then converted to the acid halide and the acid halide allowed to react with *t*-butyl alcohol to yield a *t*-butyl α-(aryloxy or arylmercapto)propionate, a key intermediate compound of formula (III), *supra*.

Alternatively, the α-halopropionic acid can be added to an aqueous mixture of a base, for example, sodium or potassium hydroxide, and an appropriate phenol or thiophenol,

and the resulting mixture heated for a period of time sufficient to substantially complete the reaction thereof to yield the α-(aryloxy or arylmercapto)propionic acid in the form of its sodium or potassium salt. By acidifying the mixture with, for example, concentrated aqueous hydrochloric acid, the corresponding free acid can be conveniently obtained. The α-(aryloxy or arylmercapto)propionic acid thus obtained can be conveniently converted to its *t*-butyl ester as previously outlined above.

The key intermediate, the *t*-butyl α-(aryloxy or arylmercapto)propionate, is conveniently aralkylated with an appropriate benzyl halide in the presence of an alkali metal amide in excess liquid ammonia to yield a *t*-butyl α-methyl-α-(aryloxy or arylmercapto)hydrocinnamate of formula (II) *supra*. Suitable alkali metal amides include sodium amide, potassium amide, and lithium amide. The ester obtained by this reaction is hydrolyzed with dilute aqueous acid to yield the desired α-methyl-α-(aryloxy or arylmercapto)hydrocinnamic acid.

In a specific example of the synthesis, ethyl α-bromopropionate is allowed to react with a mixture of *p*-chlorothiophenol, potassium carbonate, and acetone at reflux temperature overnight to yield ethyl α-(4-chlorophenylmercapto)propionate.

While the ethyl ester is preferred at this stage of the synthesis because it may be more easily purified by distillation, if desired, than the *t*-butyl ester, the *t*-butyl ester is preferred in the next step of the reaction, because fewer undesired by-products are formed when it is used. Therefore, the ethyl ester is hydrolyzed by refluxing overnight in a dilute solution of potassium hydroxide in ethanol. The hydrolysis mixture is acidified to precipitate the α-(4-chlorophenylmercapto) propionic acid, which is filtered off, converted to α - (4 - chlorophenylmercapto)propionyl chloride by reaction with thionyl chloride, and allowed to react with *t*-butyl alcohol to yield *t*-butyl α-(4-chlorophenylmercapto)-propionate.

This ester is then conveniently aralkylated by allowing it to react with benzyl chloride in the presence of potassium amide in an excess of liquid ammonia to yield *t*-butyl α-methyl - α - (4 - chlorophenylmercapto) hydrocinnamate, which is hydrolyzed by refluxing overnight in a mixture of aqueous 10 percent hydrochloric acid and aqueous 50 percent acetic acid to yield α-methyl-α-(4-chlorophenylmercapto)hydrocinnamic acid.

Where R is hydrogen in the generic formula (III), *supra*, the same general method of preparation previously described is carried out, but with different starting materials. An appropriate phenol or thiophenol is allowed to react with *t*-butyl chloroacetate in the presence of potassium carbonate and a suitable solvent such as acetone to yield the *t*-butyl (aryloxy or arylmercapto)acetate.

This ester is aralkylated with a suitable benzyl halide in the presence of lithium amide in liquid ammonia to yield the *t*-butyl α - (aryloxy or arylmercapto)hydrocinnamate. The latter ester in turn can be conveniently hydrolyzed in the same manner as previously described hereinabove using a mixture of dilute (e.g., 10 percent) aqueous hydrochloric acid and aqueous 50 percent acetic acid to yield the desired α-(aryloxy or arylmercapto)hydrocinnamic acid of formula (I), *supra*, when R is hydrogen.

The following examples describe in detail certain compounds illustrative of the present invention and methods devised for the preparation thereof.

EXAMPLE 1

t-Butyl α-(4-chlorophenylmercapto) propionate

To a mixture of 216 g. (1.5 moles) of *p*-chlorothiophenol, 276 g. of potassium carbonate, and 1100 ml. of acetone, stirred and heated to refluxing, were added dropwise 271 g. (1.5 moles) of ethyl α-bromopropionate; and the reaction mixture was stirred and refluxed overnight.

The reaction product mixture was cooled and the solid material which separated was filtered off. The filtrate was concentrated. The solid material obtained thereby was dissolved in water and the aqueous solution was extracted three times with 500 ml. portions of ether and the ether extracts combined with the concentrated filtrate. The aqueous layer was acidified and extracted with the ether. All the organic layers were combined and washed successively with 500 ml. of water, 100 ml. of aqueous 5 percent sodium hydroxide, and 500 ml. of water, dried, concentrated *in vacuo*, and distilled to yield ethyl α - (4 - chlorophenylmercapto)propionate having a boiling point of about 93—94°C. at 0.01 mm. Yield: 347 g.

A mixture of 347 g. of the ester, supra, 700 ml. of ethanol and 400 ml. of 10 percent aqueous potassium hydroxide was refluxed overnight. The reaction product mixture was cooled, and concentrated to dryness, and the residue was dissolved in 500 ml. of water and extracted twice with 300 ml. portions of ether to remove the unreacted ester. The aqueous basic layer was acidified with aqueous concentrated hydrochloric acid and extracted with ether. The ether layer was washed with water to a neutral pH, dried, and concentrated to dryness *in vacuo*. The solid residue thus obtained was recrystallized from a mixture of petroleum ether and ether to yield α-(4-chlorophenylmercapto)propionic acid having

a melting point of about 102.5—103°C. Yield: 283.6 g.

A mixture of 283.6 g. (1.31 moles) of α-(4-chlorophenylmercapto)propionic acid and 180 g. (1.5 moles) of thionyl chloride in 600 ml. of chloroform was refluxed for a time to prepare the acid chloride. The solvent and the excess thionyl chloride were removed *in vacuo* and the crude acid chloride was added to a cooled solution of 500 ml. of *t*-butyl alcohol containing 103 g. of pyridine. The reaction mixture was refluxed for two hours, cooled, dissolved in ether, and the ether solution washed successively with 500 ml. of water, 125 ml. of aqueous 5 percent sodium hydroxide solution, and 500 ml. of water, dried, and the solvent removed *in vacuo*. The residue was distilled to yield *t*-butyl α-(4-chlorophenylmercapto)propionate having a boiling point of about 104—105°C. at 0.03 mm. Yield: 294.1 g. n_D^{24}=1.5279—1.5290.

Following this same general procedure and using the appropriate starting materials, the following compounds were prepared:

t-Butyl α - (4 - chlorophenoxy)propionate. Boiling point: 98—100°C. at 0.03 mm.

t-Butyl α - (phenoxy)propionate. Boiling point: 85—86°C. at 0.04 mm. n_D^{24}=1.4810.

t-Butyl α - (*p* - tolyloxy)propionate. Boiling point: 101—102°C. at 0.8 mm. n_D^{24}=1.4840.

t-Butyl α - (*m* - chlorophenoxy)propionate. Boiling point: 89—90°C. at 0.04 mm. n_D^2=1.4909.

Example 2

α-Methyl-α-(4-chlorophenylmercapto) hydrocinnamic acid

To lithium amide prepared from 6.9 g. (1.08 gram-atom) of lithium and an excess of liquid ammonia was added an ether solution of 294.1 g. (1.08 moles) of *t*-butyl α-(4-chlorophenylmercapto)propionate and the mixture stirred for about 15 minutes. To the resulting mixture was added rapidly with caution an ether solution of 126.5 g. (1.08 moles) of benzyl chloride followed by a liter of anhydrous ether, and the reaction mixture was stirred overnight. A small amount of ethanol (50 ml.) was added to the reaction product mixture to decompose unreacted lithium amide, and the reaction mixture was dissolved in about 500 ml. of ether. The ether solution was washed successively with 200 ml. of water, 250 ml. of aqueous 5 per cent sodium hydroxide solution, and 500 ml. of water, then dried and concentrated to dryness. The crude residue was then hydrolyzed using a mixture of 1000 ml. of 50 percent aqueous acetic acid and 500 ml. of aqueous 10 percent hydrochloric acid by refluxing overnight.

The reaction product mixture was cooled and extracted with ether. The ether layer was extracted with 750 ml. of aqueous 5 percent sodium hydroxide and 500 ml. of water. The combined aqueous extracts were acidified with aqueous concentrated hydrochloric acid. The white solid which separated was extracted with ether. The ether layer was washed to neutrality with distilled water, dried, and concentrated *in vacuo* to dryness leaving a solid residue. The solid residue thus obtained was recrystallized from a mixture of ether and petroleum ether to yield α -methyl - α - (4 - chlorophenylmercapto) hydrocinnamic acid, having a melting point of about 120.5—122.5°C.

To 70 ml. of aqueous 1N sodium hydroxide solution were added 21.46 g. of α-methyl-α - (4 - chlorophenylmercapto)hydrocinnamic acid with stirring. The mixture was warmed to about 45—50°C. and filtered through a heated sintered-glass funnel. The filtrate was cooled to about 5°C. and the crystalline material which separated was collected on a chilled sintered-glass funnel and washed three times with 15 ml. portions of cold distilled water. The crystalline product was dried in vacuo for 24 hours at about 50°C. The product had a melting point of about 286—294°C. and was identified by potentiometric titration and elemental analysis as the sodium salt of α-methyl-α-(4-chlorophenylmercapto)hydrocinnamic acid.

Following the same general procedure as in Example 2 and using appropriate starting materials, the following compounds were prepared:

α - Methyl - α - (4 - chlorophenoxy)-hydrocinnamic acid. Melting point: 100.5—101.5°C.

α - Methyl - α - (4 - chlorophenoxy) - 4 - methylhydrocinnamic acid. Melting point: 118—119.5°C.

α - Methyl - α - (*p* - tolyloxy)hydrocinnamic acid. Melting point: 78—79°C.

α - Methyl - α - (3 - chlorophenoxy) hydrocinnamic acid. Melting point: 111.5—113°C.

α - Methyl - α - (4 - phenylphenoxy) - hydrocinnamic acid. Melting point: 143—145°C.

α - Methyl - α - (4 - chlorophenoxy) - 4 - methoxyhydrocinnamic acid. Melting point: 75—77°C.

α - Methyl - α - (4 - chlorophenoxy) - 4 - chlorohydrocinnamic acid. Melting point: 60—62°C.

α - Methyl - α - (4 - methoxyphenoxy) - hydrocinnamic acid. Melting point: 83—84°C.

Example 3

t-Butyl (4-chlorophenylmercapto)acetate

To a mixture of 144.8 g. (1 mole) of *p*-chlorothiophenol, 200 g. of potassium carbonate, and 600 ml. of acetone stirred and heated to refluxing were added dropwise 150.6 g. (1 mole) of *t*-butyl chloroacetate;

and the reaction mixture was stirred and refluxed overnight.

The reaction product mixture was cooled and the solid material which separated was filtered off and discarded. The filtrate was concentrated to dryness at reduced pressure, the residue thereby obtained dissolved in 700 ml. of ether, the solution washed successively with 500 ml. of water and 250 ml. of aqueous 5 percent sodium hydroxide solution. The washed solution was dried, concentrated, and distilled to yield *t*-butyl (4-chlorophenylmercapto)acetate having a boiling point of about 97—99°C./0.03 mm.; $n_D^{24}=1.5398$. Yield: 105.1 g.

Following the same general procedure, the following *t*-butyl esters were prepared:

t-Butyl (*p*-tolyloxy)acetate. Boiling point: 80—81°C. at 0.05 mm. $n_D^{24}=1.4995$.

t-Butyl (phenoxy)acetate. Boiling point: 82—83°C. at 0.01 mm. $n_D^{24}=1.4920$.

t-Butyl (*o*-chlorophenoxy)acetate. Melting point: 61.5—64°C.

t-Butyl (*p*-anisyloxy)acetate. Boiling point: 86—88°C. at 0.01 mm.

t-Butyl (*m*-chlorophenoxy)acetate. Boiling point: 77—78°C. at 0.01 mm. $n_D^{24}=1.5077$.

t-Butyl (2,4-dichlorophenoxy)acetate. Boiling point: 106—108°C. at 0.01 mm. $n_D^{24}=1.5161$.

t-Butyl (*p*-tolylmercapto)acetate. Boiling point: 111—112°C. at 0.05 mm. $n_D^{24}=1.5248$.

t-Butyl (4-chlorophenoxy)acetate. Identified by n.m.r. spectrum.

Example 4

t-Butyl ester of α-(4-chlorophenylmercapto)hydrocinnamic acid

To potassium amide prepared from 13 g. (0.34 gram-atom) of potassium and an excess of liquid ammonia was added an ether solution of 100 g. (0.34 mole) of *t*-butyl (4-chlorophenylmercapto)acetate, and the mixture was stirred for about 15 minutes. To the resulting mixture was added rapidly with caution an ether solution of 43 g. (0.34 mole) of benzyl chloride followed by a liter of anhydrous ether, and the reaction mixture was stirred overnight. A small amount of ethanol (50 ml.) was added to the reaction product mixture to decompose unreacted potassium amide and the reaction mixture was dissolved in about 500 ml. of ether. The ether solution was washed successively with 200 ml. of water, 250 ml. of aqueous 5 percent sodium hydroxide solution, and 500 ml. of water, dried, and concentrated at reduced pressure to leave a residue of the *t*-butyl ester of α-(4-chlorophenylmercapto)-hydrocinnamic acid.

Using the general procedure above, followed by hyrolyzing the tertiary-butyl ester, the following compounds were prepared:

α - (2,4 - Dichlorophenoxy)hydrocinnamic acid. Melting point: 86.5—89°C.

α - (4 -Phenylphenoxy)hydrocinnamic acid. Melting point: 152—153.5°C.

Example 5

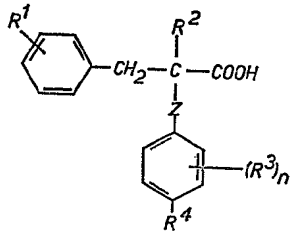
2-Diethylaminoethyl α-methyl-α-(4-chlorophenoxy)hydrocinnamate hydrochloride

A mixture of 14.5 g. (0.05 mole) of α-methyl - α - (4 - chlorophenoxy)hydrocinnamic acid, 9.5 g. (0.08 mole) of thionyl chloride and 250 ml. of chloroform was refluxed overnight, cooled, concentrated *in vacuo*, and flushed twice with 200 ml. of benzene to yield α-methyl-α-(4-chlorophenoxy)hydrocinnamoyl chloride.

The crude α-methyl-α-(4-chlorophenoxy)-hydrocinnamoyl chloride thus obtained, dissolved in 50 ml. of dry benzene, was added to a refluxing benzene solution of 8.7 g. (0.06 mole) of β-diethylaminoethanol. The reaction mixture was refluxed for about 6 hours, cooled, and dissolved in 250 ml. of benzene. This benzene solution was washed successively with 100 ml. of water, 100 ml. of a saturated aqueous sodium bicarbonate solution, and 100 ml. of water, dried, and concentrated *in vacuo* to remove the benzene solvent. The residual material was dissolved in 250 ml. of ether and the ether solution saturated with anhydrous hydrogen chloride. The solid precipitate which formed was filtered off and recrystallized from a mixture of ethanol and ether to yield 2-diethylaminoethyl α - methyl - α - (4 - chlorophenoxy) - hydrocinnamate hydrochloride as a solid, having a melting point of about 53—55°C.

WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein

R^1 is hydrogen, a halogen atom or a C_1—C_4 alkyl or C_1—C_4 alkoxy group;

R^2 is hydrogen or a methyl group;

R^3 is a halogen atom;

n is 0 or 1;

R^4 is hydrogen, a halogen atom or a C_1—C_4 alkyl, C_1—C_4 alkoxy, phenyl or phenoxy group; and

Z is oxygen or sulfur;

the salts thereof with alkali metals or alkaline earth metals, or ammonium salts thereof; and

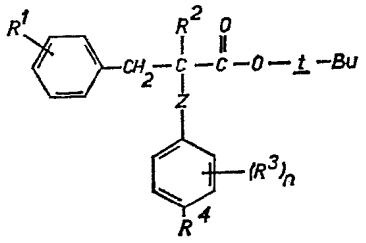
the C_1—C_4 alkyl or di(C_1—C_4 alkyl)amino-C_1—C_4 alkyl esters thereof, excluding the 2-dimethylaminoethyl ester of α-phenoxyhydrocinnamic acid and excluding the free-acid compound when n is 1 and R^2 and R^4 are hydrogen and the free-acid compound when n is 0, R^2 is hydrogen and R^4 is halogen.

2. α - Methyl α - (4 - chlorophenylmercapto)hydrocinnamic acid.

3. The sodium salt of α-methyl-α-(4-chlorophenylmercapto)hydrocinnamic acid.

4. α - Methyl - α - (4 - chlorophenoxy) - hydrocinnamic acid.

5. An ester of the formula:



wherein

R^1 is hydrogen, a halogen atom or a C_1—C_4 alkyl or C_1—C_4 alkoxy group;

R^2 is hydrogen or a methyl group;

R^3 is a halogen atom;

n is 0 or 1;

R^4 is hydrogen, a halogen atom or a C_1—C_4 alkyl, C_1—C_4 alkoxy, phenyl or phenoxy group;

Z is oxygen or sulfur; and

t-Bu represents a tertiary-butyl radical.

6. A pharmaceutical composition comprising a compound of claim 1 in admixture with a pharmaceutically acceptable carrier.

7. A process for preparing α-substituted hydrocinnamic acids of the formula in claim 1 and salts and esters thereof as defined in claim 1 which comprises hydrolyzing an ester as defined in claim 5, and if desired converting the resulting acid into a salt or ester thereof of the class defined in claim 1.

8. A process according to claim 7, in which said ester as defined in claim 5 is prepared by mixing an alkali metal amide and a benzyl halide in an inert organic solvent with a *t*-butyl α-(aryloxy)propionate, *t*-butyl α-(arylmercapto)propionate, *t*-butyl aryloxyacetate, or *t*-butyl arylmercaptoacetate, and exposing the resulting mixture to about ambient room temperature for a time sufficient to complete the reaction thereof.

9. A process according to claim 8 in which the *t*-butyl α-(aryloxy)propionate, *t*-butyl α-(arylmercapto)propionate, *t*-butyl aryloxyacetate or *t*-butyl arylmercaptoacetate is formed by reacting an appropriate phenol or thiophenol in the presence of a base and an inert solvent with an appropriate C_1—C_4 alkyl α-halopropionate, α-halopropionic acid or *t*-butyl chloroacetate.

10. The process of making the new chemical compounds of claim 1 or 5 substantially as herein described with particular reference to any one of the specific examples.

11. The products obtained by the process of any of claims 8—10.

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Chartered Patent Agents,
Agents for the Applicant(s).

Reference has been directed in pursuance of Section 9, sub-section (1) of the Patents Act, 1949, to patent No. 1,098,111.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25, Southampton Buildings, London W.C.2, from which copies may be obtained.